

Acute Myocardial Infarction

Clinical Application of Technetium 99m Stannous Pyrophosphate Infarct Scintigraphy

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Acute myocardial infarction is being recognized as a spectrum of clinical subsets. This appreciation has been brought about to a large degree by the development of several new tools that can be applied clinically to aid in evaluation of patients with acute infarction, and in some cases to provide short- and long-term prognostic information. In the realm of noninvasive methods, several tests utilizing radiopharmaceuticals and scintillation cameras have emerged and are rapidly becoming reliable diagnostic parameters in patients with coronary disease and infarction. Technetium 99m (stannous) pyrophosphate (TcPYP) scintigraphy, one of the first of these techniques to find clinical use, has been shown to be an accurate indicator of acute transmural myocardial infarction and provides added sensitivity and specificity to the diagnosis. Increased diagnostic accuracy, the dimension of visible localization and the potential for infarct sizing promise physicians better understanding of a patient's clinical presentation and a more rational approach to management.

THE DIAGNOSIS of acute myocardial infarction can be made frequently from the characteristic clinical presentation. However, additional criteria have improved upon the accuracy of this diagnosis in both the classical as well as the more subtle or complicated cases. The development of new measures for use in diagnosis and treatment of infarction have been facilitated by modern theoretical

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and technological advances. The development of a reliable electrocardiogram and diagnostic criteria for its clinical use¹⁻³ was the first of these important advances. Later in the century the recognition and utilization of muscle enzyme elevations in the serum of infarction patients^{4,5} allowed improved diagnostic sensitivity and specificity. The subsequent introduction of the myocardial specific (MB) fraction of creatine phosphokinase (CPK)⁶⁻⁷ provided an additional increment of specificity to infarct diagnosis. However, the extreme sensitivity of the enzymatic method,⁸ the temporal pattern of enzyme release⁹ and the biological factors governing serum enzyme levels¹⁰ present limitations even to this sophisticated diagnostic method. Paralleling these developments was the recognition of the prognostic implications of infarct localization and sizing.¹¹ However, neither electrocardiographic methods nor serum

ABBREVIATIONS USED IN TEXT

CPK = creatine phosphokinase
 MB = myocardial specific CPK
^{99m}Tc = technetium 99m
 TcPYP = technetium 99m (stannous)
 pyrophosphate

enzyme analysis have been able to reliably provide this important dimension of acute myocardial infarction.

While detection of experimental myocardial infarction using radiopharmaceuticals had been suggested in the early 1960's,¹² much of the current interest in clinical myocardial infarction scintigraphy was stimulated in 1973 by Bonte and co-workers.¹³ These investigators showed in dogs that technetium 99m stannous pyrophosphate (TcPYP), already in common use as a bone imaging agent,¹⁴ would localize in acutely infarcted myocardium. The use of skeletal imaging agents for infarct labeling was, in turn, partly based upon earlier work by D'Agostino¹⁵ and Shen,¹⁶ who described calcium accumulation in myocardial cells that had undergone necrosis. Since this early work in dogs, a good deal of laboratory and clinical experience with TcPYP infarct scintigraphy has been accumulated. Infarct scintigraphy has been shown to be diagnostic when conventional methods are unreliable or unavailable. Scintigraphy provides infarct visibility and may be the method of choice for noninvasive infarct localization and sizing in the clinical setting. However, controversy still exists regarding the full spectrum of its experimental and clinical utility and, therefore, its full impact on the management of patients with acute myocardial infarction. In the following text we review what is known of the biologic basis for TcPYP infarct imaging, the method for carrying out infarct scintigraphy and the range of its clinical application, and promising areas of clinical research now being investigated.

Infarct Labeling Imaging Agents

Most of the radiopharmaceuticals found to localize in acutely infarcted myocardium that have been investigated for clinical applications have been compounds of technetium 99m (^{99m}Tc). Although gallium 67 citrate has been shown also to localize in acutely infarcted myocardium,¹⁷ it requires a one- to two-day interval between injection and imaging to allow adequate soft tis-

sue clearance for infarct delineation, while its relatively high energy of emission and poor energy spectrum burdens the patient with a high radiation dose.

The use of ^{99m}Tc as a tracer in medicine was originally suggested because of its optimal physical properties.¹⁸ Later introduced into clinical medicine as an imaging agent by Harper and co-workers,¹⁹ this agent has subsequently been widely used for clinical scintigraphy. This popularity stems primarily from the abundance of its 140 KeV gamma photon emission, highly favorable for imaging by commercially available scintillation cameras; relatively short six-hour half-life, facilitating decreased radiation exposure; and favorable decay scheme, with an excellent parent-daughter relationship⁶ allowing production from molybdenum 99 generators permitting ready supply of the radiopharmaceutical.²⁰ While several chelates of technetium have been developed to image infarction, pyrophosphate appears to be the most useful of these infarct localizing radionuclides. Technetium 99m tetracycline was popularized by Holman and colleagues²¹ and was shown to provide a qualitative estimation of acute myocardial infarction size. However, areas of acute infarction can only be identified by focal myocardial deposition of the radionuclide at least 24 hours following its intravenous administration, making early assessment of infarction impossible and notably decreasing the radioactivity available for imaging. In addition, hepatic uptake of the radionuclide and a relatively low infarct-to-background radioactivity ratio diminish the accuracy and utility of this complex. Technetium 99m glucoheptinate localizes in acute infarction early, allowing optimal images to be obtained within hours after the event.²² However, hepatic labeling, relatively low infarct-to-background radioactivity ratios and inability to image the infarct late following the acute event are characteristics that may limit widespread acceptance of this technetium chelate. A variety of other phosphate compounds have similarly failed to show clinical advantage over pyrophosphate.²³⁻²⁵

Mechanisms of Myocardial TcPYP Accumulation

Relationship to Cellular Events

Intramycocardial TcPYP accumulation in pathological amounts has been shown in several studies to be confined to regions of irreversible myocardial damage.^{26,27} Extensive histopathologic ex-

aminations, mostly in acutely infarcted dogs, shows calcium and hydroxyapatite-like spicules in association with mitochondria, but also in other subcellular loci.^{26,28} Originally thought to parallel this calcium accumulation, TcPYP uptake was found not to be reduced in necrotic hearts cultured in calcium-free medium.²⁹ Although phagocytosis of the radiopharmaceutical by leukocytes migrating into the infarct was also suspected of playing a role in tracer accumulation, recent evidence has shown this also to be unlikely.²⁶

Relationship to Blood Flow

Although at higher levels of blood flow, TcPYP uptake seems to parallel the density of myocardial necrosis, Zaret and co-workers²⁸ and others³⁰ showed a low TcPYP uptake regardless of the extent of cell damage below a critical level of blood flow at approximately 30 to 40 percent of normal. Based in part on such experimental findings, it seems that the uptake of TcPYP into acutely infarcted myocardium, resulting in most cases from transient or permanent coronary occlusion, is related to residual and collateral blood flow to the area. Scintigraphic support for this hypothesis is provided by the so-called "doughnut" pattern of TcPYP uptake observed in dogs with proximal occlusion of the left anterior descending coronary artery where the central area of maximal necrosis and minimal blood flow is seen to have the least amount of tracer. Conversely, the peripheral zone with greater residual or collateral flow as identified by less intense necrosis shows maximal TcPYP uptake on the scintigram. This pattern has also been reported in humans with large anterior infarcts.^{27,31}

Clinical Correlation

These cellular processes and blood flow alterations do not result in positive *in vivo* images until at least 12 hours after acute coronary occlusion, although radioactivity greater than normal is present in infarct tissue samples as early as four to six hours after infarction. In most patients with infarction, cardiac radioactivity is maximum at 48 to 72 hours, becomes less intense by 6 to 7 days and is usually absent by 10 to 14 days after the event. This is probably due to the progressive replacement of necrotic myocardium by granulation tissue and scar with progressive reduction in calcium deposits in the area of damage.²⁷ Patterns of uptake, however, are somewhat variable with some patients maintaining low levels of increased

activity for several weeks and in some cases months. Persistently positive scintigrams have been reported³² and will be discussed in a later section.

Scintigraphic Methods

Technetium 99m (stannous) pyrophosphate for infarct imaging is made available by a variety of methods from inexpensive prepackaged kits, and is the same material generally used for routine skeletal scintigraphy. In our laboratory, TcPYP is prepared according to a modification of the method of Huberty and co-workers.³³ The material has a 100 to 1 ratio of pyrophosphate to stannous ions, is quite stable and in previous studies has shown less than 3 percent free ionic pertechnetate. TcPYP scintigrams are best done using 37-phototube, high resolution scintillation cameras which are commercially available as both stationary and portable units. Studies in our laboratory are done with a Searle (Searle Radiographics, Des Plaines, Illinois) Pho Gamma IV stationary or Ohio Nuclear (Ohio Nuclear, Solon, Ohio) portable camera. A dose of 15 mCi of technetium 99m tagged to 5 mg of stannous pyrophosphate is most commonly used. Following an intravenous injection, approximately 50 percent of the dose is excreted by the kidneys and 50 percent is taken up in hydroxyapatite-bearing structures, mainly bone. Imaging is best carried

TABLE 1.—Criteria for Interpretation of Technetium 99m Stannous Pyrophosphate Myocardial Scintigrams

<i>Intensity Grade</i>	
0	No accumulation of radionuclide in region of myocardium
1+	Slight, indefinite, accumulation of radionuclide in the cardiac region
2+	Definite accumulation of radionuclide in the region of the myocardium with activity less than that of ribs
3+	Definite accumulation of radionuclide in the region of the myocardium with activity equal to that of ribs
4+	Definite accumulation of radionuclide in the region of the myocardium with activity greater than that of ribs
<i>Distribution</i>	
DIFFUSE—Generalized radionuclide accumulation in the cardiac region apparently involving all aspects of the heart—without evidence of the ventricular cavity	
DISCRETE—Radionuclide accumulation in a specific region of myocardium	
<i>Final Interpretation</i>	
NEGATIVE—Intensity grade 0 to 1+	
POSITIVE—Intensity grade 2 to 4+	

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out at least two hours after intravenous radionuclide administration, allowing adequate time for blood clearance. All images are obtained in the anterior, 45 degree left anterior oblique and left lateral projections at the 140 KeV technetium 99m photo peak, employing a 20 percent window and taken to 300,000 counts. Due to the temporal factors involved in TcPYP uptake, optimal time for imaging is two to three days after the clinically suspected event.

Criteria have been established for infarct image interpretation³⁴ (Table 1). Image radioactivity is called *discrete* if it is confined to a localized cardiac region and *diffuse* if generally apparent in all regions. Diffuse image abnormalities show no photopenic evidence of the left ventricular cavity and show radioactivity from the cardiac apex to the sternum. Images are graded according to the radioactivity in the cardiac region on a scale of 0 to 4+, where 0 represents no increase in radioactivity beyond background; 1+ represents a slight, faint or indefinite increase in cardiac radioactivity beyond background; 2+ represents a definite increase in cardiac radioactivity beyond background, but less intense than bone; 3+ represents increased cardiac radioactivity beyond background and equal to bone, and 4+ represents increased radioactivity in the cardiac region more intense than bone. Images graded 0 or 1+ are called normal, while 2+ to 4+ images are called positive. Figures 1 through 3 are examples of TcPYP scintigrams illustrating negative, discretely positive and diffusely positive images.

Computer Applications

Although some groups have developed computer programs for rib subtraction and image enhancement,^{35,36} the need for image clarification is usually satisfied by obtaining multiple projections. Parkey and co-workers³⁷ estimate that image processing from this study may be helpful in only 10 to 15 percent of cases. Computer image enhancement can be useful when attempting quantitative scintigraphic analysis and infarct sizing as described below, but is otherwise most useful for display purposes. Routine infarct scintigraphy with TcPYP can be done and interpreted without computer assistance.

Sensitivity and Specificity in Acute Myocardial Infarction

The most important factor surrounding the potential routine clinical use of technetium 99m

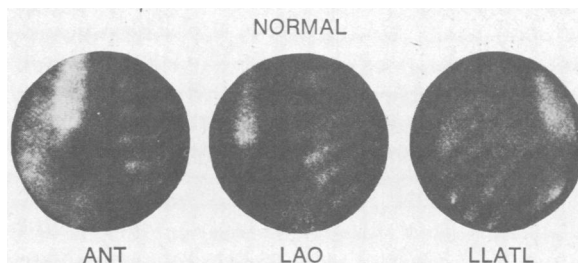


Figure 1.—Normal TcPYP scintigram. Shown are the normal scintigrams in a patient with chest pain but without acute infarction. (From Prasquier R, et al: *Circulation* 55:61-66, 1977.⁵¹ With permission of the authors and the American Heart Association.)

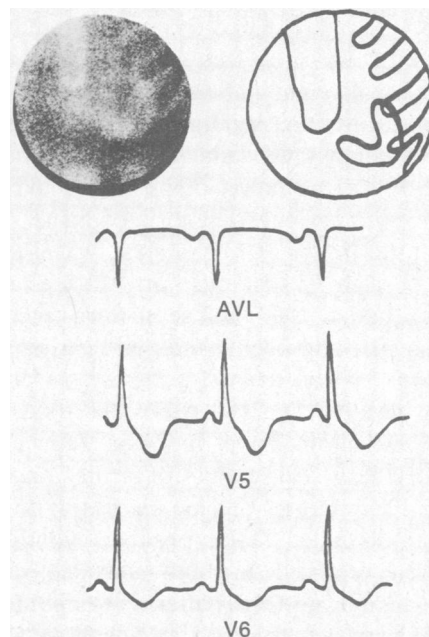


Figure 2.—Discrete positive scintigram. Above are the TcPYP scintigrams and three leads of the electrocardiogram from a patient with acute apical and anterior transmural myocardial infarction. The scintigram shows localized accumulation of radionuclide in these areas as illustrated in the schematic diagram at right. (From Botvinick EH, Shames DM: *IEEE Transactions in Nuclear Science* NS-23:1264-1267, June, 1976.⁸⁶ With permission of the authors and the IEEE.)

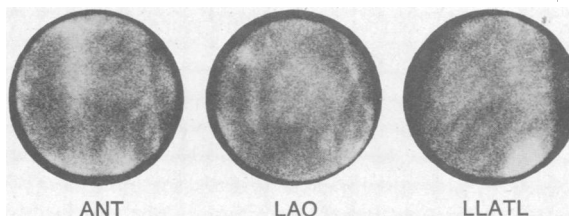


Figure 3.—Diffuse uptake. The TcPYP scintigram showing diffuse accumulation of the radionuclide in a patient with an acute subendocardial infarction. (From Prasquier R, et al: *Circulation* 55:61-66, 1977.⁵¹ With permission of the authors and the American Heart Association.)

pyrophosphate scintigraphy is the diagnostic accuracy of the test. Initial experimental work in animals documented the sensitivity of infarct scintigraphy to small amounts of tissue damage. TcPYP scintigraphy successfully identified infarction weighing more than 3 grams.^{35,38} Subsequently, Parkey and co-workers³⁴ reported the first clinical study of patients in whom acute myocardial infarction was suspected and who were admitted to a coronary care unit. They showed essentially perfect correlation with the presence of acute transmural infarction in 23 patients imaged up to eight days after the acute event. The discrete uptake of the radionuclide was appropriately correlated with the localized electrocardiographic changes. In all eight patients without other evidence of infarction, scintigrams were negative. After this report the same group described an apparent high correlation of positive scintigrams with the more difficult diagnosis of acute subendocardial infarction.³⁹ Of interest was the fact that 11 of their 17 patients with subendocardial infarction had a 2+ diffuse pattern according to criteria that had been established earlier³⁴ (see Table 1).

In the ensuing two years, however, numerous other investigators have reported reduced accuracy of these scintigrams for acute infarction. Abnormal scintigrams outside the setting of acute infarction, so-called "false positive" scintigrams, have been reported in both unstable^{40,41} and stable⁴² angina pectoris, after cardiopulmonary bypass,⁴² with left ventricular aneurysm,⁴³ with valvular calcification⁴⁴ and postcardioversion.^{45,46} Positive scans have also been described as persisting months to years following acute infarction,⁴⁷⁻⁴⁹ following left mastectomy⁴⁷⁻⁵¹ and in congestive heart failure.⁴⁹ A review of these data, however, showed that most "false positive" scintigrams were diffuse and frequently of 2+ intensity. In fact, considerable controversy has developed regarding the nature and significance of the diffuse pattern of cardiac uptake.

Diffuse Uptake

We⁵¹ evaluated more than 600 camera bone scans and myocardial scintigrams for evidence of TcPYP cardiac uptake. Among patients with clinical coronary disease, 16 percent were found to have diffuse radionuclide uptake in the cardiac region. However, a similar number of patients, 13 percent, without evidence of coronary disease also had the diffuse pattern of cardiac uptake.

The frequent visualization of femoral vasculature in bone scans of noncoronary patients with diffuse TcPYP uptake and the presence of diffuse TcPYP uptake in patients who had undergone left mastectomy and consequently had diminished left chest tissue attenuation, indicated the possibility of blood pool imaging. Although attempts to monitor radionuclide blood levels in patients with diffuse TcPYP uptake showed no significant difference when compared with normals,⁴⁷ more sensitive methods of radionuclide analysis will be required to accurately detect quantitatively small, but statistically significant, differences. Well-known factors that could potentially play a role in the production of the diffuse pattern of uptake include camera field nonuniformity, radiopharmaceutical instability, tagging inefficiency, blood clearance variations, timing postinjection and the number of days after infarction. On the other hand, since some patients with diffuse uptake have definite infarction, disregarding diffuse uptake because of its nonspecific nature could decrease test sensitivity. Berman and co-workers³⁶ have recently suggested an approach to resolving this problem. They redefined the 2+ diffuse pattern of radionuclide uptake as equivocal rather than positive for acute myocardial infarction. This resulted in a dramatic improvement in the specificity of their image interpretations. Using this scheme, they found only 3 percent false positive scintigrams in 235 patients in whom studies for possible acute infarction were carried out.

Discrete Uptake

Although there is difficulty in interpreting the diffuse pattern of uptake, there is general agreement that the discrete pattern of cardiac uptake is quite specific for the presence of acute myocardial infarction. Several lines of investigation have supported the validity of this finding. Discrete image abnormalities have been correlated with electrocardiographic abnormalities and have been shown pathologically to parallel the site of infarction.⁴¹ Additionally, the scintigraphic area of TcPYP uptake in such cases has been shown to relate favorably with infarct area and weight in animals^{27,35,38} and agrees closely with enzymatic and functional measures of infarct size in man.^{52,53} Distinguishing between discrete and diffuse uptake appears to clarify most discrepancies between the apparent accuracy of infarct scintigraphy as documented in numerous studies, with the myriad of reports of false positive scintigrams

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described earlier. This is illustrated by the information regarding the persistently positive TcPYP scintigram. Malin,⁴⁷ Lyons⁴⁹ and others^{42,48} have reported diminished specificity of TcPYP for acute infarction due to a significant number of positive images weeks and months following the acute event. Disturbed by these findings, we⁵⁴ carried out studies in 55 patients, nine days to ten years after a documented transmural infarction. In 14 of these patients imaging was done at the time of acute infarction and again at a later date. In each of the 14 patients in whom acute imaging was done, discrete scintigraphic abnormalities were noted. Among the entire group of 55 patients, 11 scintigrams remained abnormal, 9 with a diffuse pattern and 2 with discrete TcPYP uptake. In both patients with discrete uptake and in several with the diffuse pattern on remote images, a left ventricular aneurysm was found on angiographic evaluation. Therefore, discrete uptake occurred rarely in this study of remote infarction and when present was always related to a wall motion abnormality. Conversely, diffuse uptake was neither sensitive to, nor specific for, acute infarction—a finding similar to our overall experience. Previous investigators also reported

a large percentage of both left ventricular aneurysm and diffuse uptake in their cases of persistent scintigraphic positivity. Studies by Ahmad and co-workers^{42,43} while corroborating the overall accuracy of the discrete pattern of uptake for acute transmural infarction, also found a large percentage of patients with left ventricular aneurysm to have discrete radionuclide accumulation and suggested this as a possible cause of remotely positive scintigrams. Others have reported the occurrence of abnormal scintigrams in patients with left ventricular wall motion abnormalities and unstable angina pectoris.^{55,56} In most cases, these nonspecific scintigraphic abnormalities were diffuse. The exact significance of TcPYP accumulation in these abnormalities is not certain, but may represent radionuclide deposition in regions of focal calcification or in spotty areas of myocardial necrosis, either at the aneurysm perimeter or, more widely, through an ischemic zone as suggested initially by Willerson.³⁹ Figure 4 shows complete scintigraphic clearing in a patient five weeks after an acute inferior infarction. Figure 5 shows the continued presence of diffuse uptake in the scintigram done in a patient ten weeks after a documented anterior infarction. Fig-

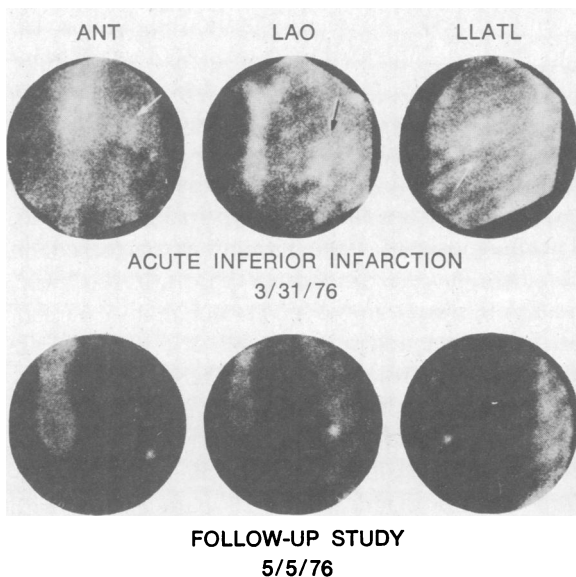


Figure 4.—Remote infarction. **Above (upper panel)** are the TcPYP scintigrams in the anterior (ANT), left anterior (LAO) and left lateral (LLATL) projections done at the time of acute inferior infarction. The scintigram is abnormal with a 3+ discrete inferior accumulation (**arrows**). In the **lower panel** are the scintigrams done in the same patient five weeks later. The patient was asymptomatic at the time of follow-up study and the image was normal with the exception of a persistent punctate rib abnormality.

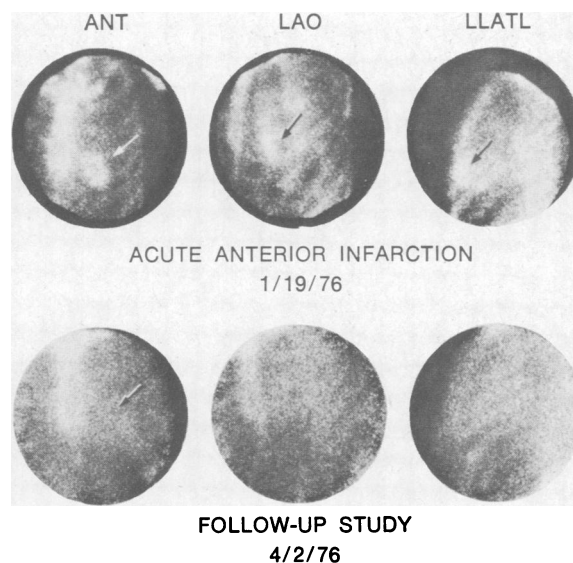


Figure 5.—Remnant diffuse uptake. **Above (upper panel)** are the TcPYP scintigrams in the anterior (ANT), left anterior oblique (LAO) and left lateral (LLATL) projections done at the time of acute anterior infarction. The scintigram is abnormal with a 4+ discrete anterior accumulation (**arrows**). In the lower panel are scintigrams done in the same patient three months later. The patient was asymptomatic at the time of repeat study, but a poorly localized 2+ diffuse pattern of radionuclide uptake was noted.

ure 6 shows the continued presence of a discrete scintigraphic abnormality 18 months after a documented anteroapical infarction. In both the patients concerned in Figures 5 and 6, left ventricular aneurysms were noted on angiography in the site of previous infarction.

Clinical Settings for Reduced Accuracy

"False positive" scintigrams related to discrete TcPYP uptake are not a common occurrence in the experience of most workers. Localized TcPYP uptake in the absence of acute infarction or associated left ventricular aneurysm has been reported with valvular calcification,⁵⁷ pericarditis,⁵⁸ tumor infiltration,⁵⁹ and penetrating and nonpenetrating trauma to the heart (J. T. Willerson, personal communication). Many of these conditions are related to myocardial necrosis, although not related to an acute coronary event.

Occasionally, scintigrams will be reported negative simply owing to the relation of the acute event to the time of imaging. Scintigrams reported negative, but done earlier than 24 hours after the event, should be repeated between two and three days after the event. Scintigrams which are negative, but done later than 1 week after the event, cannot exclude the diagnosis of acute in-

farction. On the other hand, an abnormal finding on an image done to document an acute infarction, but in the presence of a known remote infarction, must be clarified. The image abnormalities in the latter case can be related to the acute or remote infarction by correlating its location to the site and sequence of electrocardiographic abnormalities or by noting scintigraphic changes with serial images. Scintigraphic abnormalities associated with an acute infarction are more likely to be grade 3 and 4+, and will be found to be intense early and to fade when imaged serially, whereas abnormalities related to a remote event tend to persist unchanged. Such technical factors and other causes of "false positive" scintigrams must always be considered.

Clinical Applications

Impact on Infarct Diagnosis:

Transmural and Subendocardial Infarction

The availability of portable scintillation cameras and the simplicity of the technique make infarct scintigraphy feasible in community hospitals as well as major medical centers. Clinicians should demand, however, that the improvement in infarct diagnosis and evaluation be sufficient to justify the additional expense.

In an attempt to determine more quantitatively the relative clinical importance of TcPYP scintigraphy and its impact on the diagnosis of acute infarction, we reviewed⁶⁰ the records of 128 consecutive patients evaluated for possible transmural infarction or subendocardial infarction in our hospital from January 1975 to January 1976. The diagnosis of acute infarction was based on conventional electrocardiographic criteria, enzymatic criteria (CPK-MB of greater than 5 percent of total CPK) and scintigraphic criteria (discrete TcPYP myocardial uptake). Transmural infarction with new electrocardiographic Q waves was found in 35 patients, 32 with CPK-MB elevation and 34 with positive images. Subendocardial infarction was diagnosed in 28 patients, 27 with CPK-MB elevations. Seven of these 28 (25 percent) had positive TcPYP scintigrams. All of the 65 patients judged at discharge not to have infarction had negative scintigrams. It is important to note, however, that in 62 of these 65 patients there were new but nondiagnostic electrocardiographic changes or conduction abnormalities and in 30 patients there was elevated total CPK, usually related to a surgical procedure or intramuscular injection while in hospital. In 18 pa-

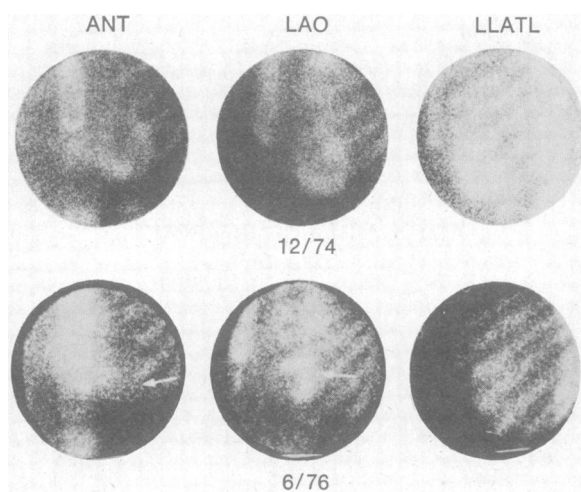


Figure 6.—Remnant discrete uptake. **Above (upper panel)** are the TcPYP scintigrams in the anterior (ANT), left anterior oblique (LAO) and left lateral (LLATL) projections done at the time of acute anteroapical infarction. The scintigram is abnormal with a discrete 3 to 4+ accumulation in the anterior wall and apex of the left ventricle. **Lower panel**, scintigrams done in the same patient 18 months later are shown. Although less intense than on the earlier study, the image remains abnormal with a similar 2 to 3+ accumulation (**arrows**). Measured acute infarct size was large and there was a documented anterior aneurysm.

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tients, 8 with transmural infarction, 2 with subendocardial infarction and 8 without infarction, there was elevated CPK-MB related to cardiac surgical procedures, cardiac catheterization, direct current countershock or myositis. Appropriately timed electrocardiograms or studies of cardiac enzymes had not been done in 12 patients, 2 with transmural infarction, 2 with subendocardial infarction and 8 without infarction, who arrived in the coronary care unit several days after the suspected event. Diffuse TcPYP uptake (2 to 4+) was found in 15 patients, 5 with subendocardial infarction and 10 without infarction. The data from this study were substantially confirmed by several subsequent studies on selected groups of infarct patients reviewed below and similar data for sensitivity and specificity were obtained recently by Berman and colleagues.³⁶ In an overall group of suspected infarct patients, therefore, TcPYP infarct scintigraphy seemed to be of greatest value in patients in whom there were non-specific electrocardiographic or enzyme abnormalities (or both), or in patients seen a few days after the suspected event. In our study, a positive scintigram was in fact the earliest objective diagnostic indicator of infarction in some cases and as such was helpful in facilitating patient management and coronary care utilization.

Subendocardial Infarction

The subset of patients with possible subendocardial infarction is frequently a particularly troublesome diagnostic group. However, accurate detection could be of considerable prognostic importance. To determine the utility of TcPYP in this group, we evaluated the diagnostic accuracy of TcPYP in 29 patients with subendocardial infarction, 47 patients with transmural infarction and 41 patients with stable angina pectoris and no infarction. The same conventional criteria for diagnosis of infarction were used as in the previous study and scintigrams were done two to six days after the event. Our results are depicted in Table 2. Considering both the discrete and diffuse patterns of TcPYP uptake as positive for acute infarction, only 38 percent with subendocardial infarction were detected, compared with 90 percent with transmural infarction ($p < .001$). However, the discrete pattern was specific for infarction when compared with the group with only stable angina pectoris ($p < .01$). Other investigators have confirmed the somewhat decreased though variable sensitivity of the TcPYP

TABLE 2.—Comparative Diagnostic Accuracy of TcPYP Scintigraphy For Acute Myocardial Infarction

	SEI	TMI	SAP
Number of patients	29	47	41
Negative	18	5	37
Diffuse uptake	6	3	4
Discrete uptake	5	39	0
SEI = subendocardial infarction			
TMI = transmural infarction			
SAP = stable angina pectoris (no infarction)			

scintigram for the diagnosis of subendocardial infarction. Sensitivities vary in these studies from 40 percent to as high as 90 percent,³⁹ a difference probably related to infarct mass and image interpretation.

Evaluation Postcardioversion

Patients in whom cardioversion or defibrillation has been carried out, frequently because of unexpected hemodynamic collapse or in survivors of out-of-hospital sudden death, represent another group of patients in whom the presence or exclusion of acute infarction is of considerable importance for both acute and chronic management. Yet this group is frequently difficult to classify with certainty due to persistently abnormal cardiac enzymes and electrocardiograms related to the often traumatic resuscitative efforts or abnormal electrocardiograms due to previous infarction or conduction abnormalities. Although it was initially anticipated that the TcPYP scintigram might be of diagnostic use in this setting, several investigators reported findings, mostly in animals, suggesting that the TcPYP scintigram may be falsely positive due to the countershock alone.^{45,46} In a recent study of 44 patients in whom direct current countershock was carried out at our institution, we did not find this to be the case.⁶¹ The discrete positive TcPYP scintigram reliably distinguished between those patients who had suffered an acute infarction by other criteria from those who had not. Although electrically induced myocardial necrosis resulting in radionuclide uptake and also artificially induced chest wall uptake are legitimate concerns and may in fact occur when high dose repetitive discharges are delivered, in the clinical setting over a wide range of electrical energies and patient sizes, the discrete pattern of TcPYP uptake remained a discriminating and useful indicator of infarction.

Infarct Localization

The important dimension of visible localization

is provided by TcPYP scintigraphy in patients with acute infarction. Localization is relatively easy with 3 and 4+ discrete scintigrams, but is also possible with less intense uptake. In addition to the conventional three projections discussed in an earlier section, occasionally other degrees of obliquity will be added when heart location or rotation in the chest is unusual or TcPYP uptake in another projection cannot otherwise be localized. The sternum, spine and ribs are visualized and the location of myocardial uptake relative to these landmarks is noted. Hence, anterior wall infarction rotates with the sternum as the camera rotates more laterally. Conversely, posterior wall infarction, which can look similar to anterior infarction on the anterior projection, rotates away from the sternum. Inferior wall infarction visualizes as a plate-like extension of activity from the xiphisternum leftward as seen in the anterior projection. Figure 7 shows the utility of multiple projections in localizing acute anterior and inferior infarctions. Confirmation of appropriately rotating myocardial activity in multiple projections adds considerable security to the diagnosis. A great deal of care must be taken in interpretation of TcPYP activity that is less intense or seen in only one projection. Such noncardiac

activity most frequently leads to misdiagnosis and additional views or computer enhancement may be of some aid. Subendocardial infarctions, when resulting in a positive scintigram, may be considerably more difficult to localize, but may be dramatic, as illustrated in Figures 8 and 9.

Infarct Extension

Recurrent chest pain or clinical deterioration (or both) following acute infarction can result from continuing necrosis and extension of infarction. This can at times be difficult to differentiate from other clinical entities including pulmonary embolism or the postmyocardial infarction syndrome.⁶² Scintigraphy done shortly after the occurrence of symptoms can be diagnostic

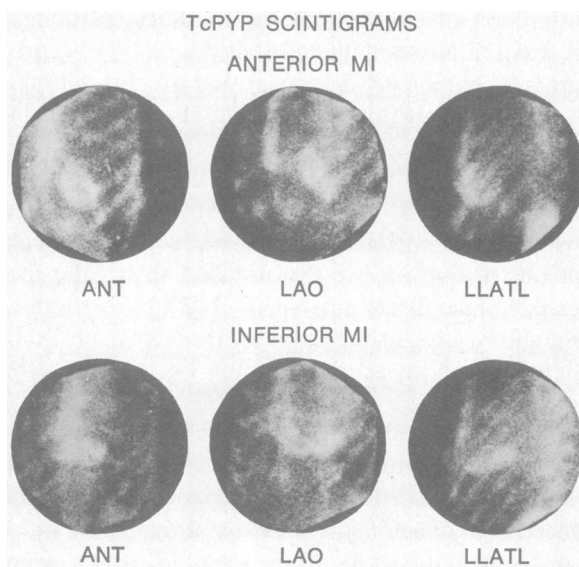


Figure 7.—Discrete uptake. Illustrated is discrete TcPYP uptake in patients with acute anterior (upper panel) and inferior (lower panel) transmural myocardial infarctions (MI). Note that radionuclide accumulation rotates with the sternum in the anterior infarction. The inferior infarction has a plate-like extension of radioactivity from the sternum leftward. In both cases, localization is enhanced with the use of multiple projections.

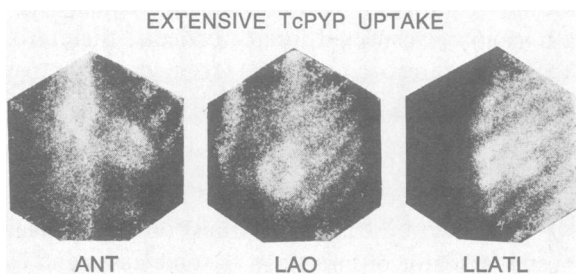


Figure 8.—Extensive TcPYP uptake. The scintigram above shows extensive intramyocardial radionuclide accumulation in a patient with massive acute subendocardial infarction. The presence of the photopenic left ventricular cavity confirms the myocardial localization and separates the study from those with diffuse uptake. In this patient total CPK was more than 1,000 units with 65 percent CPK-MB. However, the patient presented with only mild congestive heart failure which responded quickly to therapy.

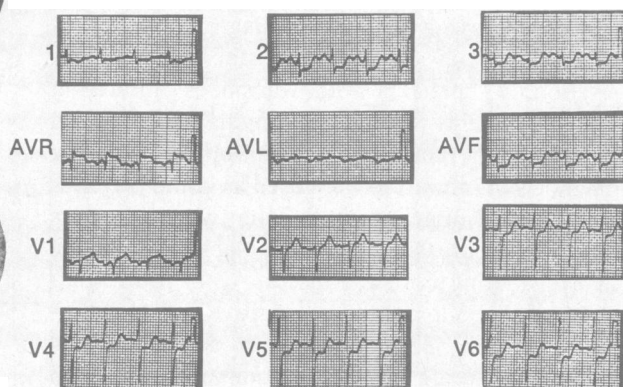


Figure 9.—Electrocardiographic correlation. Shown above is the electrocardiogram of the patient in Figure 8. Seen are widespread ischemic ST segment depressions which persisted. Diagnostic Q waves did not evolve. The maintenance of moderately good cardiac function in the presence of extensive necrosis may relate to the subendocardial distribution of damage.

for infarction as illustrated in Figure 10. The presence of an earlier scintigram documenting the infarct pattern of the original insult improves the diagnostic value of succeeding studies, both while the patient is still in hospital and during any subsequent events months or years later. Characterization of the infarction in this way and in association with other scintigraphic methods can help develop the full picture of the extent of irreversibly necrotic or reversibly ischemic myocardium (see below).

Right Ventricular Involvement

Acute infarction of the right ventricle, either exclusively or together with the left ventricular inferior wall, may be of considerable importance both diagnostically and therapeutically.⁶³ We⁶⁴ carried out studies in 26 patients with documented transmural infarction. Of 15 patients with inferior

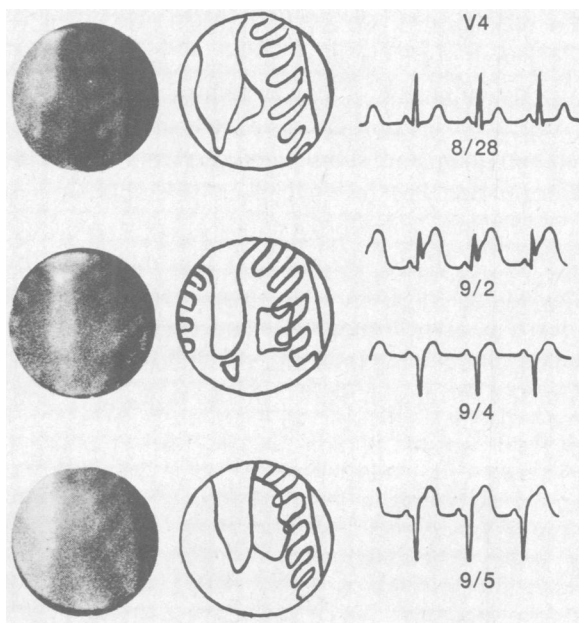


Figure 10.—Infarct extension. Shown are the TcPYP scintigrams from a patient initially admitted with chest pain and a normal electrocardiogram. The upper scintigram, done at admission, shows faint, diffuse uptake in the cardiac region. Intermittent chest pain continued and five days later the electrocardiogram showed acute injury and subsequent definite anterior and lateral infarction. The corresponding scintigram (**middle panel**) now shows a larger area of intense and discrete cardiac uptake. Chest pain resolved but subsequently returned with renewed ST segment elevation and ventricular ectopy. The scintigram done at that time (**lower panel**) documents a large discrete abnormality, considerably more extensive than previously and represented infarct extension. (From Shames DM, Botvinick EH: IEEE Transactions in Nuclear Science NS-23: 1237-1242, June, 1976.⁸⁵ With permission of the authors and the IEEE.)

infarction by all criteria, including TcPYP scintigraphy, there was additional discrete uptake localized to the right ventricular free wall and often the inferior aspect of the interventricular septum in 5 patients. Gated blood pool scintigraphy, echocardiography and bedside hemodynamics by right heart catheterization using a triple lumen catheter, confirmed abnormal right ventricular size and function consistent with right ventricular infarction. The importance of these findings is considerable. Right ventricular infarction seems to occur more frequently than might be anticipated and when present is primarily responsible for the hemodynamic derangements seen and dictates specific therapeutic approaches which can be life saving. Patients with significant right ventricular infarction frequently present with low cardiac output and elevated systemic venous pressures due almost entirely to right ventricular pump failure. The clinical features can be confused with pericardial tamponade or more commonly cardiogenic shock due to left heart failure. In fact, the left ventricle in these cases can be relatively intact, but unable to maintain forward output due to volume starvation and may exhibit normal or low filling pressures. Standard diuretic therapy in this situation could exacerbate rather than improve the hemodynamic picture by further diminishing left ventricular filling and consequent cardiac output. Hence, right ventricular infarction can be masked in the initial clinical presentation and its quick noninvasive diagnosis by TcPYP scintigraphy represents an exciting advance in aiding management of these patients. Figure 11 compares the scintigraphic findings in two patients with inferior infarction, one with right ventricular involvement.

Perioperative Infarction

The diagnosis of perioperative myocardial infarction, especially in patients in whom coronary artery bypass surgical procedures are being done, can be uncertain. Although in the absence of previous infarction, new electrocardiographic Q waves appear to be a specific finding for perioperative infarction,^{65,66} many patients will in fact have antecedent infarction, conduction abnormalities or nonspecific repolarization changes on both preoperative and postoperative electrocardiograms. Similarly, findings in previous studies^{44,66,67} have suggested that even the MB fraction of CPK may be present in the serum post-

operatively in the absence of clinically apparent infarction.

To evaluate the application of TcPYP infarct scintigraphy to the diagnosis of infarction following myocardial revascularization, we⁶⁸ obtained postoperative scintigrams, serial electrocardiograms and cardiac specific enzymes in 10 control and 51 revascularized patients. In all control patients electrocardiograms and scintigrams were negative for infarction, but in eight there were abnormal findings on studies of isoenzymes done after surgical operation. In eight revascularized patients there were diagnostic electrocardiograms, scintigrams and enzyme studies, but in two patients in whom postoperative scintigrams and enzyme studies were positive there were negative electrocardiograms. In 34 patients in whom postoperative electrocardiograms and scintigrams were negative, there were positive findings on isoenzyme studies, and in only 7 patients were all test results negative. Our data suggest that infarct scintigraphy is a useful adjunct to electrocardiograms for the diagnosis of perioperative infarction following revascularization. Similar conclusions were noted by Righetti and co-workers.^{44,66} In both studies preoperative TcPYP scintigrams appeared helpful in gauging the

presence of myocardial damage as well as for postoperative comparison. Figure 12 shows the positive infarct scintigram in a patient with an apical and lateral perioperative infarction. In this case enzymes were only mildly elevated and the electrocardiogram, although evolving new Q waves, became diagnostic only several days following scintigraphic infarct documentation and clinical deterioration.

Research Implications

Infarct Sizing

Death from acute myocardial infarction is a result of either arrhythmia or power failure in most cases. The advent of arrhythmia monitoring and coronary care units has reduced mortality from the former. Concomitant with this advance has been the development of intense interest in understanding the syndrome of power failure and its mechanisms. Several important reports have documented the relationship of infarct size to the development of power failure and, also, an inverse correlation between estimates of infarct size in man and subsequent survival.^{11,69,70} This information has resulted in considerable activity concentrated on therapeutic interventions designed to limit the size of the infarction by salvaging ischemic but presumably not yet necrotic myocardium.^{71,72} To objectively determine infarct prognosis and the effect of interventions, one must have a reliable repeatable non-

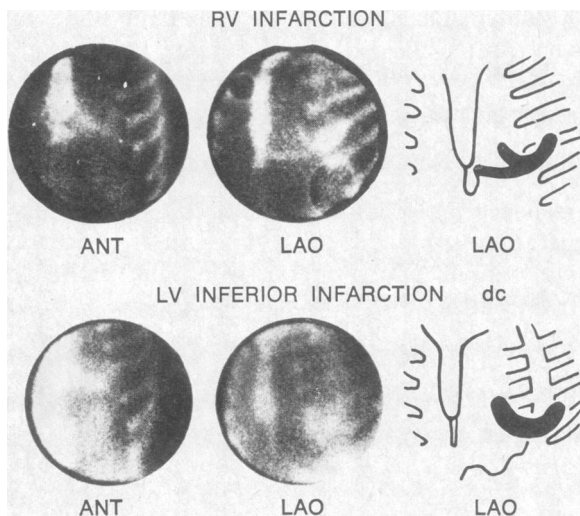


Figure 11.—Right ventricular infarction. Shown above (upper panel) are scintigrams from a patient with inferior wall infarction and right ventricular involvement. TcPYP labeling is seen to involve the distal intraventricular septum and right ventricle. The latter is anterior to the septum in the left anterior oblique (LAO) projection. The lower panel shows the TcPYP scintigram in a patient with typical acute inferior infarction. The LAO projection shows inferior accumulation to be considerably more posterior and separate from anterior bony structures.

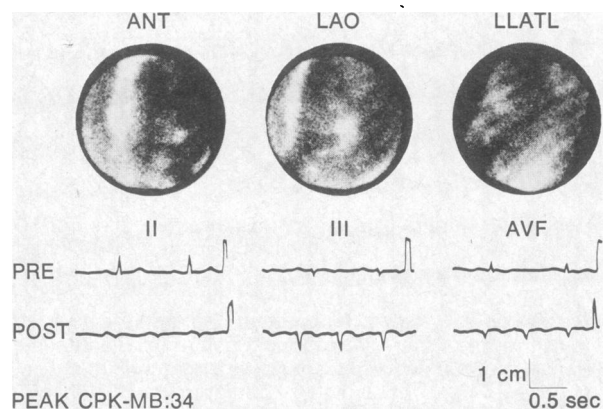


Figure 12.—Perioperative infarction. Shown are the postoperative scintigrams and representative preoperative and postoperative electrocardiograms of a patient in whom there was an inferoapical and lateral perioperative infarction. The peak CPK-MB obtained during the first two postoperative days was only 34 units. (From Klausner SC, et al: *Circulation* 56:173-180, 1977.⁶⁸ With permission of the authors and the American Heart Association.)

invasive method of measuring infarct size. To date, most commonly used methods for infarct sizing include precordial electrocardiographic ST segment mapping⁷³ and analysis of CPK serum enzyme curves.⁷⁴

Since the recognition of TcPYP uptake in acutely infarcted myocardium, several groups of investigators have attempted noninvasively to judge the size of infarcts—both experimentally produced in dogs^{35,38} and in humans.^{21,52,53,75} In our animal work³⁸ the image infarct area and count rate 48 hours after infarction correlated well with pathologic infarct area and weight. This relationship was well maintained for anterior and lateral infarctions. Image area measurements obtained in a variety of projections in animals following experimental infarction showed the largest measured infarct area to correlate well with pathologic infarct area in cases of anterior infarction. Similar good correlations have been obtained using manual and computer assisted area measurements.³⁵ Recently we⁵³ evaluated scintigraphic infarct size in 26 patients with acute infarction. There was a significant negative correlation between image infarct area and left ventricular function as measured by stroke work index and ejection fraction. Other workers⁵² have shown a relationship between infarct size as determined by CPK-MP and TcPYP image infarct area. Modifications of these methods may prove them complementary in acute infarct sizing. While non-invasive scintigraphic estimation of infarct size is an important goal,⁷⁶ it is still far removed from routine clinical application.

Other Scintigraphic Methods in Acute Myocardial Infarction

Technetium 99m pyrophosphate is a so-called "hot spot" imaging agent in that it selectively labels the area of interest—in this case, acutely infarcted myocardium. At present, it must be considered the scintigraphic technique of choice for this clinical purpose in spite of the limitations discussed. Potassium 43, rubidium 81 and more recently thallium 201 are intracellular cations which concentrate rapidly in viable, intact myocardial cells in relation to myocardial perfusion following intravenous administration and allow imaging in this initial distribution for approximately one hour after injection. Thallium 201⁷⁷⁻⁷⁹ is the most commonly used agent due to its convenient 73-hour physical half-life and major 70 to 80 KeV emission. A significant coronary

stenosis in one or more of the major coronary arteries producing a zone of relative ischemia at stress will result in decreased relative radioactivity in that area of myocardium when the radionuclide is administered during stress.⁸⁰ Similarly, at rest, scar will result in a "cold spot" due to decreased uptake of the radionuclide in the affected area. While this radionuclide is most commonly employed in association with stress testing to bring out an area of relative underperfusion due to coronary artery stenosis,^{81,82} it is also used in some centers as an acute infarct imaging agent. Wackers⁸³ has recently demonstrated that thallium 201 scintigraphy is an extremely sensitive test for acute infarction early in the course, but gradually loses its sensitivity six hours or more after the event. However, a thallium 201 scintigram, when positive in the acute setting, cannot differentiate ischemia from infarction or fresh from remote infarction. Thallium 201 scintigraphy done with the patient at rest, weeks to months after the event, differs from TcPYP scintigraphy also in its inability to differentiate remote infarction. In the acute setting, thallium 201 presumably is identifying acutely ischemic myocardium in addition to the infarcted area, whereas TcPYP does not appear to produce positive scintigrams in ischemic but not infarcted myocardium.^{26,27,57} Abnormalities on thallium 201 perfusion scintigrams are not specific for acute infarction, previous infarction or reversible ischemia, but must be correlated clinically. Correlation of abnormalities seen on a perfusion scintigram with those seen on a TcPYP scintigram may aid the identification of those patients who would be most benefited by aggressive therapeutic intervention. A patient presenting with power failure in the setting of his first myocardial infarction may present with a small TcPYP abnormality. Identification of a large concomitant perfusion defect would indicate that the functional decompensation was largely attributable to a large surrounding area of ischemic and perhaps salvageable myocardium and would be evidence in favor of aggressive treatment. Figure 13 shows infarct and perfusion scintigrams done on the same patient with acute inferior infarction.

In contrast to previously discussed methods, blood pool labeling with technetium 99m albumin or other complexes is primarily used as a non-invasive ventriculogram. This study allows a variety of measurements of ventricular size and motion.⁸⁴ With a computer, ventricular function

curves can be analyzed. Such noninvasive analysis of infarct patients will aid quantification of their functional disability and when done in association with other scintigraphic methods will identify the magnitude of loss related to reversible or irreversible conditions. Illustrating the combined use of these radionuclide procedures is a patient (Figures 8 and 9) in whom there was an extensive acute subendocardial infarction. This was documented by the development of the highest CPK-MB elevations seen in our institution during the past two years and serial electrocardiograms which showed sustained ST segment depression without the evolution of Q waves. The infarct area, as estimated from the extensive TcPYP seen on the scintigram, could well have been expected in a patient near death with cardiogenic shock. In fact, the patient was admitted with only mild congestive heart failure and improved rapidly using conventional therapy. A gated equilibrium radionuclide ventriculogram done soon after admission showed only mild, yet generalized, contraction abnormalities which correlated more closely with the patient's clinical presentation and course than the other scintigraphic measurements and helped us considerably

in understanding the patient's clinical syndrome. Possibly, extensive myocardial damage in this case was related to relatively mild functional difficulty due to the subendocardial distribution of necrosis. Such cases further emphasize the heterogeneous spectrum of acute myocardial infarction. The correlation of information obtained from these scintigraphic procedures together with electrocardiographic and enzymatic data will lead to our greater understanding of the clinical subsets of this disease.

Conclusions

Technetium 99m infarct scintigraphy represents a new and exciting approach to the diagnosis and characterization of acute myocardial infarction. The discrete pattern of uptake is both sensitive and specific for acute infarction. TcPYP appears less sensitive to subendocardial infarction, but when seen in the discrete pattern is diagnostic. Discrete TcPYP abnormalities outside of the setting of acute infarction are infrequent, but may occur in patients with heavy valve calcification, calcified pericardium and left ventricular aneurysm. The diffuse pattern of uptake is nonspecific. Clinical experience to date has shown TcPYP scintigraphy to be particularly helpful for infarct identification where the usual studies are nondiagnostic, unreliable or unavailable. The clinical value of scintigrams appears greatest in patients in whom there are electrocardiographic or enzymatic ambiguities—after cardioversion or cardiac surgical procedures, for example—and in patients with suspected infarct extension or involvement of the right ventricle. TcPYP scintigraphy has potential use in infarct sizing and therefore as a guide to acute infarct intervention. With other scintigraphic methods, TcPYP scintigraphy helps to differentiate reversibly from irreversibly damaged myocardium and in so doing aids physicians in understanding the full implications of the clinical syndrome of acute infarction, facilitating the institution of optimal therapy.⁸⁵⁻⁸⁶

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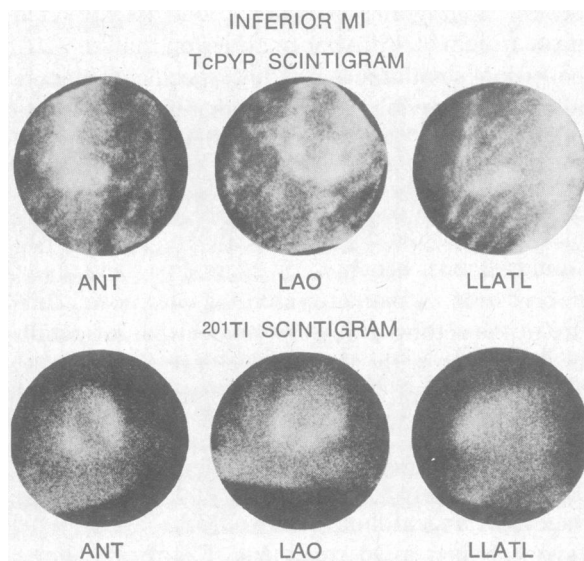


Figure 13.—Combined imaging. Shown in the upper panel are the TcPYP infarct scintigrams from a patient with acute transmural inferior infarction. There is a plate-like accumulation of radionuclide extending leftward from the sternum. The lower panel shows the TI-201 scintigrams done at rest in the same patient. An area of relative hypoperfusion involving the inferior left ventricular wall is noted in all three projections and corresponds to the area of discrete TcPYP uptake in the infarct scintigram.

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Handling a Hypoestronemic Teenager

With a teenager who might be hypoestronemic who comes in and says, "I want to have a good flow—I just don't like being different from the other girls. . . . What kinds of hormones do you use?" I've got a problem . . . I wouldn't treat her, and she'd find another doctor. Because if I put her on a temperature chart and she was ovulating, there would be no reason for me to treat her and I would suggest that she might see someone else whose feelings were different. My counseling would be: (1) Let's find out if you're ovulating and (2) If you're ovulating, then Mother Nature has allowed you in a lucky fashion to have hypomenorrheic flows. When you want to get pregnant, look at how lucky you've been—your iron reserves are great.

—ALVIN F. GOLDFARB, MD, *Philadelphia*
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